A Phase I-II Study of Tumor Vaccine Following Chemotherapy in Patients With Previously Untreated Metastatic Breast Cancer:

Vaccine-Induced Bias of T cell Repertoire Reconstitution After T cell Re-Infusion

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Metastatic breast cancer remains to this day a mostly incurable disease, with less than 10% of patients reaching a long-term disease-free survival. This study proposes to treat patients with previously untreated metastatic breast cancer using dose-intensive chemotherapy (Paclitaxel, Doxorubicin, Cyclophosphamide) followed by immune depleting chemotherapy (Fludarabine, Cyclophosphamide) at standard doses as a platform for immunotherapy (CEA vaccines).

The primary objectives are:

- Event-Free Survival (compared to the EFS in NCI historical control studies)
- Evaluate this immunization strategy biologically by assessing CEA-specific T cell responses

This study is based on the following four hypotheses and understandings:

1. Intensive chemotherapy followed by immune depleting chemotherapy can provide an effective platform for subsequent immunotherapy by:

- Lengthening the progression-free survival period, thus allowing more time for a slow acting therapy such as repeated vaccination to be effective.
- Maximally decreasing the patient's tumor burden, shown both clinically and experimentally to be desirable if not necessary for immunotherapy to be effective.
- Decreasing the tumor burden which may also decrease a tumor-induced immuno-suppressive effect linked to tumor bulk.
- Providing tumor antigen exposure in the form of repeated immunizations. This may take advantage of the pattern of immune reconstitution following profound immune depletion at early time points (antigen-driven peripheral expansion of T cells) and the renewal of a T cell repertoire biased towards tumor antigens and anti-tumor responses at later time points.

2. Low antigenicity of tumor antigens and immune tolerance may be overcome in a clinically relevant fashion by providing exposure to the tumor antigen (in our case, CEA) in a more immunogenic presentation along with an added co-stimulatory signal (in the form of two poxvirus-based recombinant vaccines containing the genes for CEA and co-stimulatory molecules).

3. Due to the post immune depletion defect and delay in immune reconstitution, an adequate immune response to vaccines may not occur unless the patients are provided, following chemotherapy, with unaltered T cells by re-infusing pre-chemotherapy lymphocytes immediately prior to vaccine boosts.

4. The late recovery of thymic function post immune depletion (18 to 24 months) with reappearance of naïve T cells may play a determinant role in the prevention of later disease progression. This is the rationale for the late series of immunizations.

Treatment Plan:
See included schema

- ***Initial immunization***:
  - before any chemotherapy on the protocol
  - single subcutaneous injection of Recombinant **Vaccinia**-CEA(6D)/TRICOM.

- ***Lymphopheresis***, 3 weeks later (To be re-infused with vaccine boosts after chemotherapy).

- ***Chemotherapy***
  - *First induction chemotherapy regimen (3 to 5 cycles):*

PACLITAXEL 160 mg/m^2 per cycle: by continuous IV infusion over 3 consecutive days, days 1- 3
CYCLOPHOSPHAMIDE 2700 mg/m^2 per cycle divided in 3 consecutive days, days 1-3

  - *Second induction chemotherapy regimen (4 cycles)*:

DOXORUBICIN 60mg/m^2 per cycle day 1
CYCLOPHOSPHAMIDE 600mg/m^2 per cycle day 1

  - *Immune Depletion (1 cycle):*

CYCLOPHOSPHAMIDE 600mg/m^2 per day for 4 consecutive days
FLUDARABINE 30 mg/m^2 per day for 4 consecutive days

- *Biphosphonate therapy, if indicated, will start with the chemotherapy*
- *Surgery and radiation, as clinically indicated, will take place before the Immune Depletion chemotherapy cycle.*
- *Hormonal therapy, if indicated, will start after all chemotherapy and radiation are completed*

- ***Re-immunizations***
  - Use the Recombinant **Fowlpox**-CEA(6D)/TRICOM.
  - An "early" series of three monthly re-immunizations. The first two are given in conjunction with lymphocyte re-infusions (starts 2 weeks after the Immune Depletion cycle)
  - Four subsequent re-immunizations, 6 months apart:
    - "intermediate" at 10 months,
    - "late 1" at 16 months,
    - "late 2" at 22 months,
    - "late 3" at 28 months.

Patient population:
Metastatic breast cancer,

- Newly diagnosed or received adjuvant chemotherapy more than 18 months prior to entry.
- **Tumor staining positive for CEA (NCI will do from pathology blocks).**
- Hormone receptor positive or negative; Her-2 overexpressed or not.

Exclusion criteria:

- Age < 18 years
- Patients in whom an urgent or emergent clinical situation does not safely allow for the short delay in initiating the "Concurrent Therapy" (as defined in section 3.2) necessary for the pre-treatment immunization and lymphocyte collection (at the discretion of the PI).
- Patients requiring chronic immunosuppressive therapy (including corticosteroids) for any medical condition.
- Patients with an autoimmune disease: autoimmune neutropenia, thrombocytopenia, or hemolytic anemia; Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren syndrome, Scleroderma, Systemic Sclerosis, Myasthenia Gravis; Multiple sclerosis, Goodpasture syndrome; Addison's disease, Hashimoto's thyroiditis, or active Graves' disease).
- Any abnormality on the following tests suggestive of an autoimmune disease: ANA, anti-DNA, T3, T4, TSH.
- Patients with active inflammatory bowel disease.
- Patients with history of clinically significant heart disease.
- Patients testing positive for HIV or hepatitis B or C.
- Patients sero-negative for EBV.
- Patients known or found to be pregnant.
- Patients of childbearing age who are unwilling to practice contraception.
- Patients with history of brain metastases.
- Patients with an active second malignancy (excluding treated skin cancers or carcinoma in-situ).
- Patients with a life expectancy reasonably estimated at less than 6 months.
- Patients may be excluded at the discretion of the PI if it is deemed that allowing participation would represent an unacceptable medical or psychiatric risk.
- History of splenectomy.
- Allergy to eggs.

Several exclusion criteria are specific to vaccinia administration:

The recombinant vaccinia vaccine should not be administered if the following apply to either recipients or, for at least two weeks after vaccination, to their close household contacts (Close household contacts are those who share housing or have close physical contact):

- Persons with active or a history of eczema or other eczematoid skin disorders.
- Persons with other acute, chronic or exfoliative skin conditions (*e.g.*, atopic dermatitis, burns, impetigo, varicella zoster, severe acne or other open rashes or wounds) until condition resolves.
- Pregnant or nursing women.
- Children under **5** years of age.
- Immunodeficient or immunosuppressed persons by disease or therapy, including HIV infection.
- History of seizures, encephalitis, or multiple sclerosis.
- History of allergy or complications with past vaccinia vaccination.

Schema of the protocol

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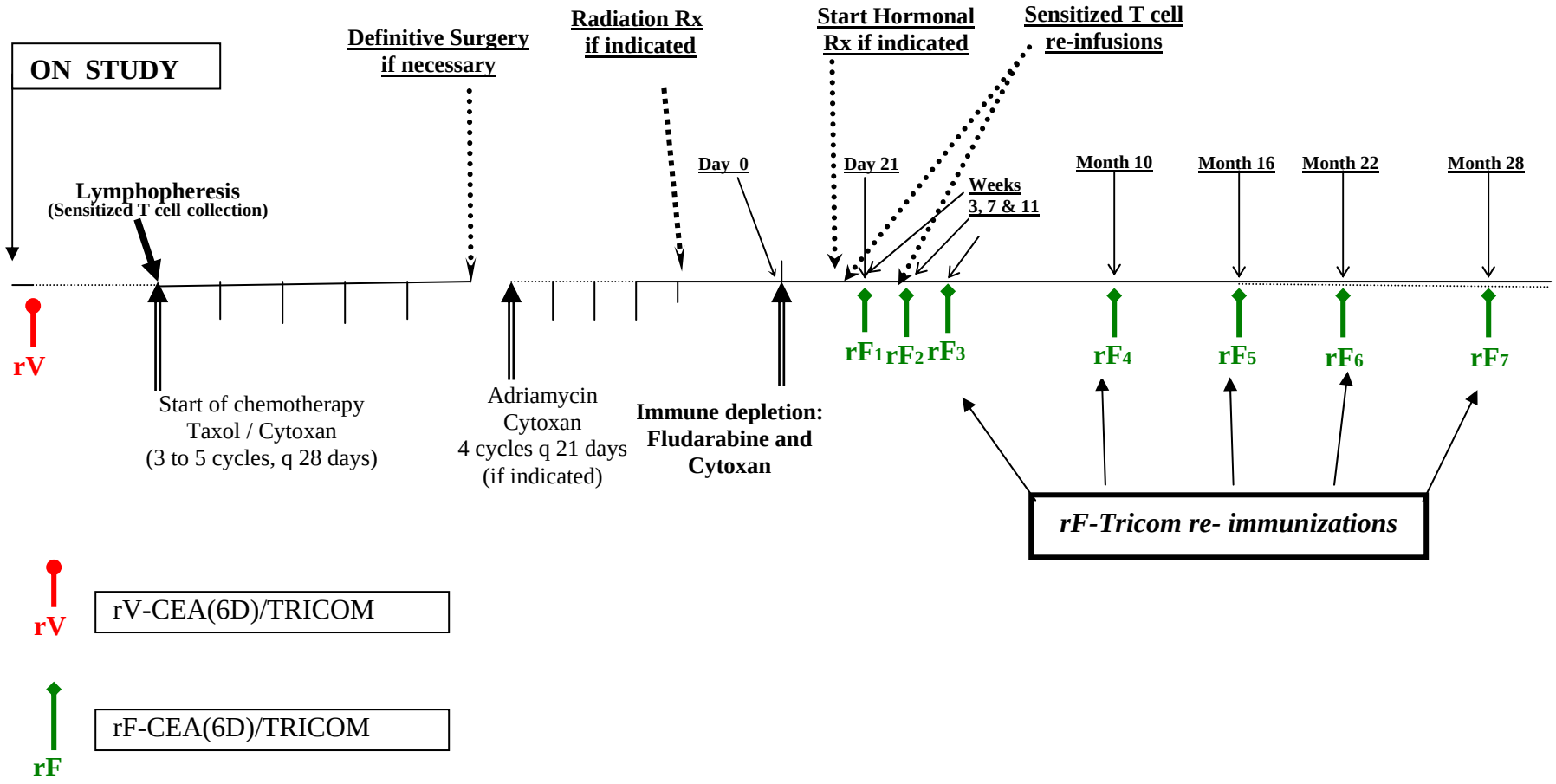

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